PHARMACOLOGY AND TOXICOLOGY

Submission of Preclinical Carcinogenicity Protocols and Study Results

CONTENTS

PURPOSE

This MAPP establishes the policies and procedures by which the Office of Review Management will receive and review submissions of carcinogenicity protocols and study results for conformity with acceptable practices. It specifically provides a mechanism for locating and tracking nonclinical information not submitted to an active investigational new drug application (IND) by allowing submission of INDs that propose no clinical protocol and are inactivated upon receipt. This policy will be in force until a general MAPP establishing a tracking system for all pre-IND submissions is published. At that time, the general MAPP will supercede this policy, which will be withdrawn.

BACKGROUND

Sponsors and FDA sometimes find it useful to discuss carcinogenicity protocol designs, dose selection, and the adequacy of ongoing or completed studies prior to the submission of an IND. FDA would like to provide opportunities for discussion and early review, but without an IND, no formal mechanism exists for tracking the submission of nonclinical information and linking the pre-IND discussions with the eventual IND/NDA.

With the advent of the International Conference on Harmonisation (ICH), international guidance has been developed to facilitate the selection of dose and study design to assess the carcinogenic potential of pharmaceutical compounds. ICH guidance encourages sponsor contact and discussion with regulatory authorities for assistance in determining when and how carcinogenicity studies should be carried out for a pharmaceutical product.

Experience has shown that collaborative efforts between FDA and sponsors on study designs produce better quality studies and reduce expenditures of resources. Therefore, the Center needs a process to provide pre-IND recommendations on dose selection and protocol design for carcinogenicity studies, as well as a method by which the recommendations can be tracked and eventually retrieved for consideration at appropriate times in clinical development.

In this MAPP, CDER explains how it will receive nonclinical proposed carcinogenicity protocols, toxicity data supporting the dose selection, and, when available, carcinogenicity study results submitted to an ongoing IND or to an inactivated IND application containing no proposed clinical studies and submitted for the sole purpose of seeking consultation on nonclinical issues. In the absence of a clinical protocol, the submission should include a request to inactivate the IND upon receipt (WI, the COMIS code for inactivate). This action (inactivation) will preclude the clinical hold action ordinarily necessitated by the lack of a clinical protocol in the IND submission. Because FDA has 30 days to review amendments to inactive INDs, it will maintain the integrity of the automatic 30-day safety review period prior to initiation of the clinical study.

REFERENCES

- Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115) (Modernization Act), November 21, 1997. *http://www.fda.gov/cder/guidance/105-115.htm#SEC. 111*

- MAPP 7412.0, Management of CDER Pharmacology/Toxicology Coordinating Committee

- MAPP 7412.1, Management of CDER Carcinogenicity Assessment Committee (CAC) and Executive CAC

- MAPP 7412.2, Distribution of Final Reports from the Carcinogenicity Assessment Committee (CAC)

- *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals*, International Conference on Harmonisation (ICH), March 1996.

- *S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals*, (ICH) March 1995.

POLICY

CDER Office of Review Management will accept the submission to an existing IND, or to an inactivated IND containing no proposed clinical protocol, of (1) proposed carcinogenicity protocol(s), (2) toxicity data supporting the proposed dose selection in the protocol, (3) carcinogenicity study results, and (4) other pertinent information. Review divisions within the Office of Review Management will use this mechanism to provide early consultative recommendations on proposed carcinogenicity study design and dose selection, as well as to review completed carcinogenicity studies for conformity with acceptable practices. If there is no existing/ongoing IND, those submissions will be designated as inactive INDs, but will be given an IND number. Such an IND should contain:

- A statement requesting a review of the proposed carcinogenicity protocol and/or completed study(s) for conformity with acceptable practices by the review division and the CAC.

- A proposed carcinogenicity protocol and data supporting the proposed protocol design and doses and/or the completed carcinogenicity study(s).

- Information sufficient to identify the proposed clinical indication.

- In the absence of an ongoing IND and clinical protocol, a written request to inactivate the IND.

All written reviews and recommendations, whether they relate to material submitted under an active or inactive IND, should be filed under the assigned IND number and communicated to the sponsor in accordance with MAPP 7412.2, Guide for Distribution of Final Reports from the Carcinogenicity Assessment Committee (CAC) and Executive CAC.

The submission of a clinical protocol and supporting nonclinical information to an inactive IND will reactivate the application. A 30-day review period in which clinical investigations under the IND may not begin will be initiated with the reactivation of the application unless FDA notifies the sponsor that the clinical investigation(s) described in the protocol may begin earlier or that the study is on clinical hold. 21 CFR 312.45 outlines the procedures for reactivation of an inactive IND application.

PROCEDURES

Central Document Room (CDR)

The CDR will process these INDs as though they were "full" INDs.

Division Document Room (DDR)

The DDR will process these INDs as though they were full INDs and will code the submission of an "n" doc (COMIS code for original submission) and WI. All three copies will be forwarded to the manager/consumer safety officer as usual.

Project Manager (PM)

If a protocol for a carcinogenicity study is submitted to an existing IND with a request for comment, the PM will follow usual division practices. A copy of the request for protocol review should be sent to the Associate Director, Pharmacology and Toxicology, Office of Review Management.

When an IND containing a proposed protocol or results of a carcinogenicity study is received as a new IND application without a clinical protocol, the PM will review the submission for an inactivation request letter from the sponsor, and, if one is included, draft and issue an inactivation letter for the application rather than a normal acknowledgment letter.

If an inactivation request is not included with the submission, the PM will contact the sponsor to confirm that the submission was intended as a nonclinical only IND for carcinogenicity study assessment, explain that such submissions should include a request for inactivation, record the conversation in a telecommunication memo, and issue an acknowledgment and inactivation letter.

Pharmacologist

When the IND submission contains a proposed carcinogenicity protocol, the reviewing pharmacologist will review the protocol(s) as well as the toxicity data supporting the proposed dose selection or the study design of the completed or ongoing studies. A review package should be made available for the Executive Carcinogenicity Assessment Committee (CAC) at least 7 days prior to the scheduled meeting of the members of the review division with the committee. If a completed carcinogenicity study is submitted to the IND with a request for review of protocol acceptability, the protocol will be evaluated in the same manner as a protocol for a proposed new study. The reviewing

pharmacologist should review the completed study results for carcinogenic findings in a timely manner (usually within 6 months of the letter date of the submission) and have a review package available for the Executive CAC at least 7 days prior to the scheduled meeting of the review division with the committee.

Carcinogenicity Assessment Committee and Executive CAC

The Executive CAC will review and evaluate the pharmacologist's review and recommendations of the proposed carcinogenicity protocol(s) and toxicity data in conjunction with the information provided by the sponsor and provide written recommendations within 45 days of the receipt stamp date (as defined in the MAPP 7412.1, Management of CDER Carcinogenicity Assessment Committee (CAC) and Executive CAC).

Review Division

The review division will provide the committee's recommendations to the sponsor according to MAPP 7412.2, Distribution of Final Reports from the Carcinogenicity Assessment Committee (CAC) and Executive CAC.

EFFECTIVE DATE

This MAPP is effective upon date of publication.